PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/004372	26.04.2004	02.05.2003

International Patent Classification (IPC) or both national classification and IPC
C07D471/08, A61K31/4995, A61P13/12, A61P9/12

Applicant
ACTELION PHARMACEUTICALS LTD

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☐ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 10-12 (with regard to industrial applicability)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1, 3-7, 9-12 (partly) are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☒ the claims, or said claims Nos. 1, 3-7, 9-12 (partly) are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 10-12 (with regard to industrial applicability)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	1-12
	No:	Claims	-
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	-

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.1 Claims 10-12 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

III.2 Claims 1, 3-7 and 9-12 relate inter alia to a group of compounds (compounds with k = 0) for which **no support** within the meaning of Art. 6 PCT and/or disclosure within the meaning od Art. 5 PCT can be found in the description. Consequently, the search was carried out only for those parts of the claims which appear to be supported an disclosed, namely the parts relating to compounds with k = 1.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 Cited documents

D1: WO 97/09311 A (HOFFMANN LA ROCHE) 13 March 1997 (1997-03-13)
D2: US-A-3 509 161 (DOLD OTTO ET AL) 28 April 1970 (1970-04-28)
D3: EL-ABBADY S A ET AL: "ENHANCED REACTIVITY OF PYRIDIN-3-OL TOWARDS 4-PHENYL-1,2,4-TRIAZOLINE 3,5-DIONE: FMO TREATMENT OF THE CYCLOADDITION PROCESS BY ASED-MO CALCULATIONS METHOD" ZAGAZIG JOURNAL OF PHARMACEUTICAL SCIENCES, FACULTY OF PHARMACY ZAGAZIG UNIVERSITY, CAIRO, EG, vol. 5, no. 1, June 1996 (1996-06), pages 68-74, XP001154254 ISSN: 1110-5089

The indicated designations will be adhered to throughout the examination procedure.

V.2 Novelty

The bicyclic systems of the D1 and the D2 compounds contain one N atom only.
In the compounds disclosed in D3, the L-corresponding moiety is different, and the structural fragments -T-Q-M and -W-V-U are missing.
Therefore the subject-matter of claim 1 and also of claims 2-12 are considered novel.

V.3 Inventive step

V.3.1 According to the description, the problem underlying the present application is to be seen in the provision of further renin-inhibitory compounds which can be used in the treatment of cardiovascular diseases and renal insufficiency.

V.3.2 D1 is considered to represent the most relevant prior art for the subject-matter of the claims on file since the compounds disclosed therein are also described to be useful in the treatment of heart and kidney insufficiency. However, the D1 compounds, if bicylic, have only one nitrogen atom as heteroatom, there is no double bond within the ring system, and the compounds have a different substitution pattern anyhow.

V.3.3 It can thus be said that the the technical problem as defined above has been solved in a non-obvious way: the structural variations compared to D1 have neither been disclosed nor foreshadowed in D1 or in any other of the cited documents.

V.3.4 Consequently, inventive step can be acknowledged for the subject-matter of claims 1-12 on file.

V.4 Industrial applicability

V.4.1 The subject-matter of claims 1-9 is industrially applicable.

V.4.2 For the assessment of the present claims 10-12 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the

manufacture of a medicament for a new medical treatment.

Re Item VI
Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 03/093267	13.11.2003	08.04.2003	29.04.2002
WO 2004/002957	08.01.2004	29.04.2003	27.06.2002

These documents were published after the priority date, but prior to the filing date of the present application. Each of these documents may become relevant with regard to novelty and/or inventive step during the regional phase before the EPO.

Re Item VIII
Certain observations on the international application

VIII.1 In claim 1, the terms "aryl", "heteroaryl", "cycloalkyl", "heterocyclyl" are not clear within the meaning of Art. 6 PCT as to the possible number of ring members and the kind of heteroatoms involved. These terms should have been properly defined according to the description, pages 6 to 8.

VIII.2 A clarity objection under Art. 6 PCT also applies to the term "lower" in connection with "alkyl", "alkenyl", "alkenylene" and "alkylene" since the reader is not informed about the maximum number of C atoms that can be present.